

Chirotope Generation – A Step Towards Multi-Conformational 3D-QSPR

Ralf Gugisch

Lehrstuhl II für Mathematik
University of Bayreuth

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Cluj-Napoca, Romania

Outline

- 1 3D-QSPR and Conformational Analysis
- 2 Orientation Functions
- 3 Chirotopes and Conformer Generation

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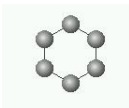
The problem with 3D-QSPR

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A chemical compound ...

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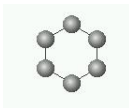
A chemical compound ...



cyclohexane

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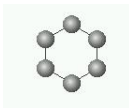


cyclohexane

... may appear in different *conformations*

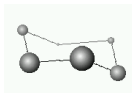
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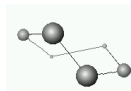


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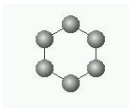
chair form



twisted form

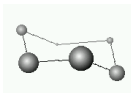
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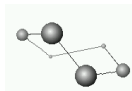


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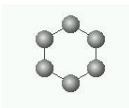


twisted form

... having different *geometric indices* (e.g. topographic Wiener index):

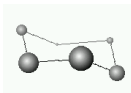
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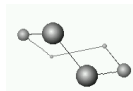


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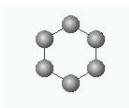
... having different *geometric indices* (e.g. topographic Wiener index):

34.44

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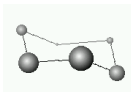
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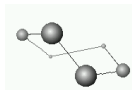


cyclohexane

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chair form



twisted form

... having different *geometric indices* (e.g. topographic Wiener index):

34.44

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It is *not* clear which conformation is responsible for the property.

The problem with 3D-QSPR

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 - by configurations of each butane substructure (gauche⁺ / gauche⁻ or anti)
 - by orientation functions (i.e. chirotopes)

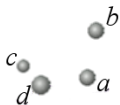
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The orientation function

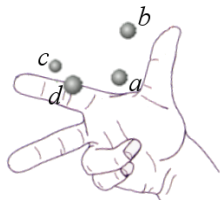
The orientation function

- The “right-hand rule”:



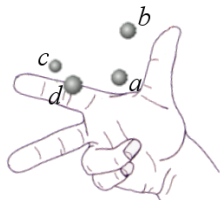
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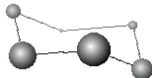


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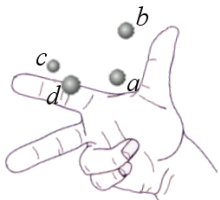


- In molecules:

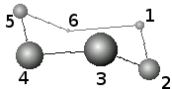


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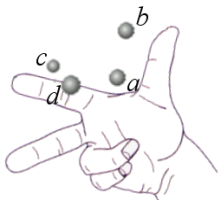


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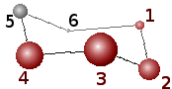


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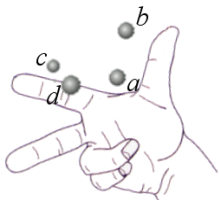


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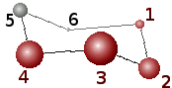


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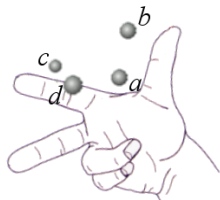
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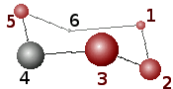
+
1234

The orientation function

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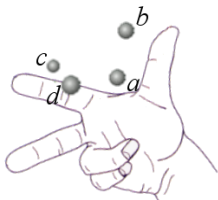
- In molecules:



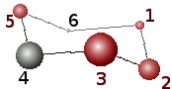
1234
+

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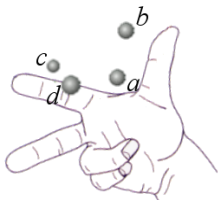


$$\begin{array}{l} 1234 \\ 1235 \end{array}$$

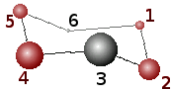
$$++$$

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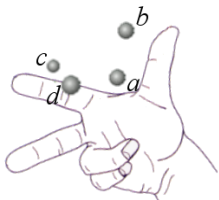


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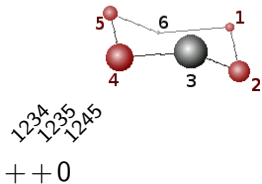
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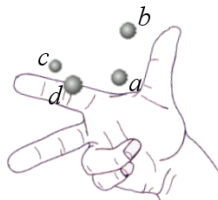


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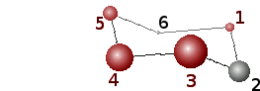


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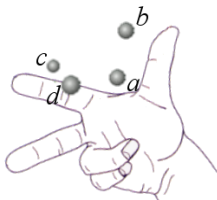
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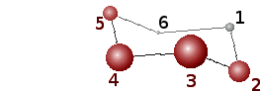
1234
1235
1245
1345
++0-

The orientation function

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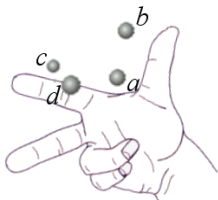


1234
1235
1245
1345
2345

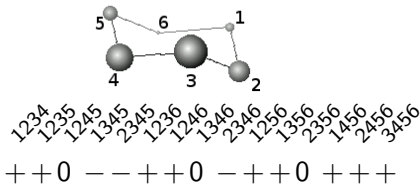
++ 0 --

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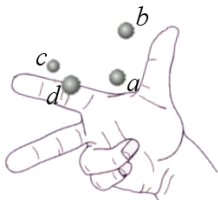


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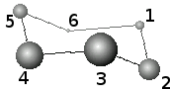


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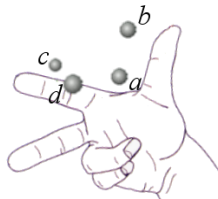


1234
1235
1245
1345
2345
1236
1246
1346
2346
1256
1356
2356
1456
2456
3456

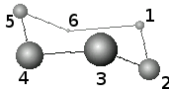
$$\chi = ++0 \quad --++0 \quad -+++0 \quad +++$$

The orientation function

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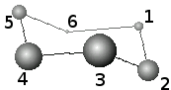


1234
1235
1245
1345
2345
1236
1246
1346
2346
1256
1356
2356
1456
2456
3456

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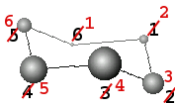
The *orientation function* χ (in combination with the molecular graph) describes a molecule on an intermediate level between constitution and conformation.

Canonical forms for orientation functions



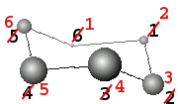
$$\chi = \begin{matrix} 1234 \\ 1235 \\ 1245 \\ 1345 \\ 2345 \\ 1236 \\ 1246 \\ 1346 \\ 2346 \\ 1256 \\ 1356 \\ 2356 \\ 1456 \\ 2456 \\ 3456 \end{matrix} \quad \begin{matrix} + + 0 & - - + + 0 & - + + 0 & + + + \end{matrix}$$

Canonical forms for orientation functions



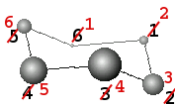
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 \chi = & ++0 & --+ & ++0 & --+ & ++0 & --+ & ++0 & --+ & ++0 & ++ & ++ & ++ & ++ & ++ & ++ \\
 & --0 & ++ & -- & --0 & ++ & -- & --0 & ++ & -- & --0 & -- & -- & -- & -- & --
 \end{array}$$

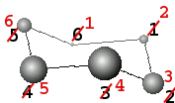
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 & --0 & ++- & --0 & ++- & --0 & ++- & --0 & -- & -- & -- & -- & -- & -- & --
 \end{array}$$

- Canonical forms are important for orientation functions (as they are for the molecular graphs).

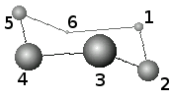
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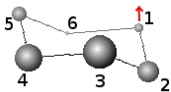
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- We are able to calculate the canonical form.

Partially defined orientation functions



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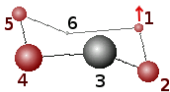
Partially defined orientation functions



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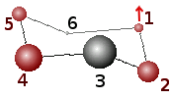
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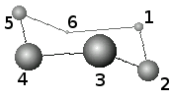
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Partially defined orientation functions



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Partially defined orientation functions

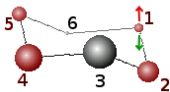


1234
1235
1245
1345
2345
1236
1246
1346
2346
1256
1356
2356
1456
2456
3456

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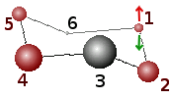


1234
1235
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1236
1246
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1256
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2356
1456
2456
3456

$$\chi = +++0 \quad --++0 \quad -+++0 \quad ++++$$

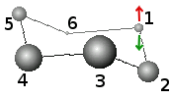
$$\chi = +++- \quad -+++ \quad -+++0 \quad ++++$$

Partially defined orientation functions



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 \chi = & +++ & - & - & +++ & - & +++ & - & +++ & 0 & & & & & &
 \end{array}$$

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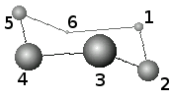
1234
1235
1245
1345
2345
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$$\chi = + + 0 \quad - - + + 0 \quad - + + 0 \quad + + +$$

$$\chi = + + + \quad - - + + + \quad - + + 0 \quad + + +$$

$$\chi = + + - \quad - - + + - \quad - + + 0 \quad + + +$$

Partially defined orientation functions



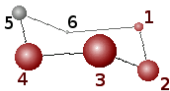
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$$\chi = + + 0 \quad - - + + 0 \quad - + + 0 \quad + + +$$

$$\chi = + + + \quad - - + + + \quad - + + 0 \quad + + +$$

$$\chi = + + - \quad - - + + - \quad - + + 0 \quad + + +$$

Partially defined orientation functions



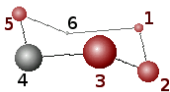
1234
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$$\chi = + + 0 \quad - - + + 0 \quad - + + 0 \quad + + +$$

$$\chi = + + + - - + + + - + + 0 \quad + + +$$

$$\chi = + + - - - + + - - + + 0 \quad + + +$$

Partially defined orientation functions



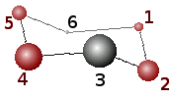
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$$\chi = + + 0 \quad - - + + 0 \quad - + + 0 \quad + + +$$

$$\chi = + + + \quad - - + + + \quad - + + 0 \quad + + +$$

$$\chi = + + - \quad - - - + + - \quad - + + 0 \quad + + +$$

Partially defined orientation functions



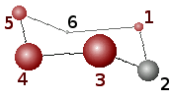
1234
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$$\chi = ++0 \quad --++0 \quad -+++0 \quad ++++$$

$$\chi = ++\color{red}+ \quad --++++ \quad -+++0 \quad ++++$$

$$\chi = ++\color{red}- \quad --++-- \quad -+++0 \quad ++++$$

Partially defined orientation functions



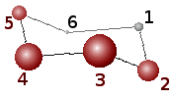
1234 1235 1245 1345 2345 1236 1246 1346 2346 1256 1356 2356 1456 2456 3456

$$\chi = \begin{matrix} ++0 & - & - & + & + & 0 & - & + & + & 0 & + & + & + & + & + & + \end{matrix}$$

$$\chi = \begin{matrix} + & + & + & - & - & + & + & + & - & + & + & 0 & + & + & + & + \end{matrix}$$

$$\chi = \begin{matrix} + & + & - & - & - & + & + & - & - & + & + & 0 & + & + & + & + \end{matrix}$$

Partially defined orientation functions



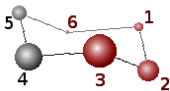
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$$\chi = ++0 \quad - \quad - \quad ++0 \quad -++0 \quad +++$$

$$\chi = +++ \quad - \quad - \quad +++ \quad -++0 \quad +++$$

$$\chi = ++ \quad - \quad - \quad - \quad ++ \quad - \quad - \quad ++0 \quad +++$$

Partially defined orientation functions



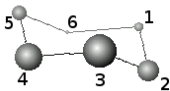
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$$\chi = ++0 \quad - \quad ++0 \quad -++0 \quad +++$$

$$\chi = +++ \quad - \quad +++ \quad -++0 \quad +++$$

$$\chi = ++ \quad - \quad - \quad ++ \quad - \quad -++0 \quad +++$$

Partially defined orientation functions



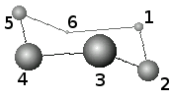
1234 1235 1245 1345 2345 1236 1246 1346 2346 1256 1356 2356 1456 2456 3456

$$\chi = ++0 \quad --++0 \quad -+++0 \quad ++++$$

$$\chi = +++- \quad -+++ \quad -+++0 \quad ++++$$

$$\chi = ++-- \quad -++- \quad -+++0 \quad ++++$$

Partially defined orientation functions



1234 1235 1245 1345 2345 1236 1246 1346 2346 1256 1356 2356 1456 2456 3456

$$\chi = ++0 \quad --++0 \quad -+++0 \quad +++$$

$$\chi = +++ \quad - - + + + \quad - + + 0 \quad +++$$

$$\chi = ++ - - - + + - - + + 0 \quad +++$$

- Partially defined orientation functions give the possibility to classify the conformations in a graduated application-specific manner.

Outline

- 1 3D-QSPR and Conformational Analysis
- 2 Orientation Functions
- 3 Chirotopes and Conformer Generation**

Conformer generation

Conformer generation

Our Strategy for conformer generation:

Conformer generation

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- Generate orientation functions.

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- Try to find a conformer for each of these mappings.

Conformer generation

Our Strategy for conformer generation:

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Question:

Which mappings $n^4 \rightarrow \{0, \pm 1\}$ are orientation functions?

Chirotope

Chirotope

A **chirotope** (of rank 4) over n points (*the atoms*) is a mapping

$$\chi : n^4 \rightarrow \{0, \pm 1\}$$

with:

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$$\chi(\mathbf{a}_{\pi^{-1}(0)}, \dots, \mathbf{a}_{\pi^{-1}(3)}) = \text{sgn}(\pi) \cdot \chi(\mathbf{a}_0, \dots, \mathbf{a}_3).$$

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- χ fulfills the binary Grassmann-Plücker relations:

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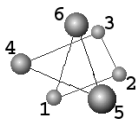
$$\chi(\vec{a}) \cdot \chi(\vec{b}) = 1 \implies \exists i \in n : \chi(b_i, a_1, \dots, a_3) \cdot \chi(b_0, \dots, \underset{\substack{\uparrow \\ i\text{-th position}}}{a_0}, \dots, b_3) = 1. \quad (\text{GP})$$

Radon partitions

- A chemical unfeasible conformation:

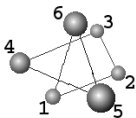
Radon partitions

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Radon partitions

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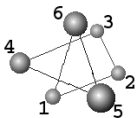


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$$\chi = + + + + + + + + + - - + + + +$$

Radon partitions

- A chemical unfeasible conformation:



1234
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$$\chi = + + + + + + + + + - - + + + +$$

Question:

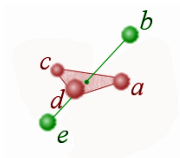
Is it possible to recognize the infeasibility from the orientation function only?

Radon partitions (2)

- A *radon partition* is a pair (A,B) of subsets of all atoms, such that their convex hulls intersect:

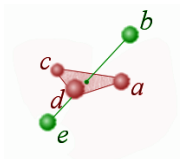
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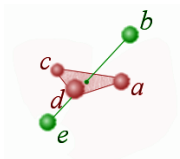
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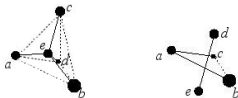
- The chirotope determines all radon partitions.

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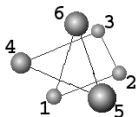


- The chirotope determines all radon partitions.
- This way, we can recognize (some) chemical unfeasible configurations, e.g.



Radon partitions

- A chemical unfeasible conformation:

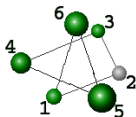


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$$\chi = + + + + + + + + - - + + + +$$

Radon partitions

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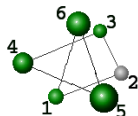


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$$\chi = + + + + + + + + - - + + + +$$

Radon partitions

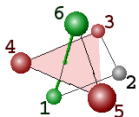
- A chemical unfeasible conformation:



$$\begin{array}{cccccccccccc}
 & & & & 6 & & & & 5 & & & & 4 & & & & 3 & & & & 1 \\
 & & & & \nearrow & & & & \nearrow & & & & \nearrow & & & & \nearrow & & & & \nearrow \\
 1234 & 1235 & 1245 & 1345 & 2345 & 1236 & 1246 & 1346 & 2346 & 1256 & 1356 & 2356 & 1456 & 2456 & 3456 \\
 \chi = & + & + & + & + & + & + & + & + & - & - & + & + & + & + \\
 & & & & + & & & & - & & & + & - & & +
 \end{array}$$

Radon partitions

- A chemical unfeasible conformation:



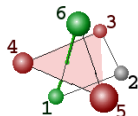
is of form



$$\begin{array}{cccccccccccc}
 & & & & 6 & & 5 & & 4 & & 3 & & 1 \\
 & & & & \nearrow & & \nearrow & & \nearrow & & \nearrow & & \nearrow \\
 1234 & 1235 & 1245 & 1345 & 2345 & 1236 & 1246 & 1346 & 2346 & 1256 & 1356 & 2356 & 1456 & 2456 & 3456 \\
 \chi = & + & + & + & + & + & + & + & - & - & + & + & + & + & + \\
 & & & & + & & & - & & + & & - & & + & \\
 & & & & & & & & & & & & & & &
 \end{array}$$

Radon partitions

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is of form



$$\begin{array}{cccccccccccc}
 & & & & 6 & & 5 & & 4 & & 3 & & 1 \\
 & & & & \nearrow & & \nearrow & & \nearrow & & \nearrow & & \nearrow \\
 1234 & 1235 & 1245 & 1345 & 2345 & 1236 & 1246 & 1346 & 2346 & 1256 & 1356 & 2356 & 1456 & 2456 & 3456 \\
 \chi = & + & + & + & + & + & + & + & - & - & + & + & + & + & + \\
 & & & & + & & - & & + & & - & & + & & +
 \end{array}$$

- We did not need coordinates nor angles for this test.

Conclusions

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Conclusions

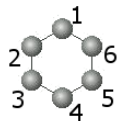
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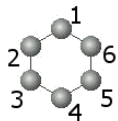
Thank You!

Conformer generation: The example cyclohexane



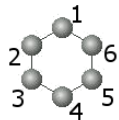
Conformer generation: The example cyclohexane

- The molecular graph has 12 automorphisms.



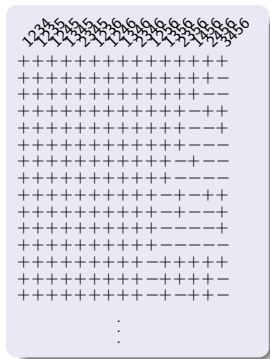
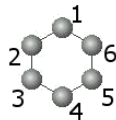
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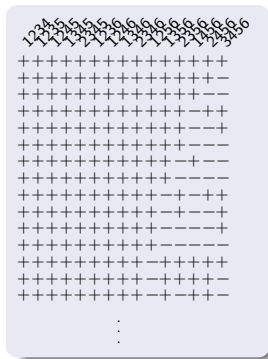
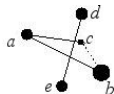
Conformer generation: The example cyclohexane

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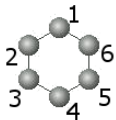
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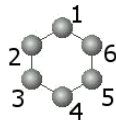


1234	1235	1236	1256	1456	3456
+	+	+	+	+	+
+	+	+	+	+	-
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+	+	+	+	+	-
+	+	+	+	-	-
+	+	+	+	-	+
+	+	+	+	-	+
+	+	+	+	-	-
+	+	+	+	-	+
+	+	+	+	-	-
+	+	+	+	-	+
+	+	+	+	-	-
+	+	+	+	-	+
+	+	+	+	-	-
+	+	+	+	-	+
+	+	+	+	-	-

⋮

Conformer generation: The example cyclohexane

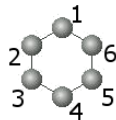
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1234	2345	1236	1256	1456	3456
+	+	+	+	+	+
+	+	+	+	+	+
+	+	+	+	+	+
/	/	/	/	/	/
+	+	+	+	-	+
/	/	/	/	/	/
+	+	+	+	-	-
/	/	/	/	/	/
+	+	+	+	-	-
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/	/	/	/	/	/
+	+	+	-	+	+
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⋮					

Conformer generation: The example cyclohexane

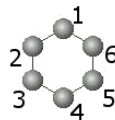
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- Restricting to quadrupels corresponding to butane substructures: **13**



1234	2345	1236	1256	1456	3456
+	+	+	+	+	+
+	+	+	+	+	-
+	+	+	+	-	+
+	+	+	+	-	-
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+	-	+	-	+	-
+	-	+	-	+	-
+	-	+	-	+	-
-	+	+	-	+	-

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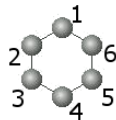
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- Conformation as local minima of an energy function were found for:



	1234	2345	1236	1256	1456	3456
1	+/	+/	+/	+/	+/	+/
2	+ +	+ +	+ +	+ +	+ +	+ -
3	+/	+/	+/	+/	+/	+/
4	+ -	+ +	+ -	+ -	+ -	- -
5	+/	+/	-	-	+/	+/
6	+/	+/	-	-	+/	+/
7	+/	+/	+/	+/	+/	+/
8	+ +	+ +	-	-	+ +	+ +
9	+/	+/	+/	+/	+/	+/
10	+ -	+ +	+ -	+ -	+ -	- -
11	+/	+/	+/	+/	+/	+/
12	+ +	+ +	-	-	+ +	+ +
13	+/	+/	+/	+/	+/	+/
14	+ -	+ +	+ -	+ -	+ -	- -
15	+/	+/	+/	+/	+/	+/
16	+ +	+ +	-	-	+ +	+ +
17	+/	+/	+/	+/	+/	+/
18	+ -	+ +	+ -	+ -	+ -	- -
19	+/	+/	+/	+/	+/	+/
20	+ +	+ +	-	-	+ +	+ +

Conformer generation: The example cyclohexane

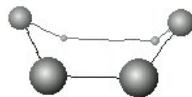
- The molecular graph has 12 automorphisms.
- We assume, that no 4 atoms are in a plane.
- We get **386** chirotopes.
- Excluding unfeasable radon partitions: **162**
- Restricting to quadrupels corresponding to butane substructures: **13**
- Conformation as local minima of an energy function were found for: **4**



1234	1245	1256	1345	1356	1456	2345	2356	2456	3456
+	+	+	+	+	+	+	+	+	-
+	+	+	+	+	+	+	+	+	-
+	+	+	+	+	+	+	+	+	+
+	+	+	+	+	+	+	+	+	-

Conformer generation: The example cyclohexane

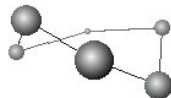
- The molecular graph has 12 automorphisms.
- We assume, that no 4 atoms are in a plane.
- We get **386** chirotopes.
- Excluding unfeasible radon partitions: **162**
- Restricting to quadrupels corresponding to butane substructures: **13**
- Conformation as local minima of an energy function were found for: **4**
 - boat form (a “sattle point”)



1234	2345	1236	1456	3456
+	+	+	+	-
+	+	+	+	-
+	+	+	+	+
+	+	+	+	+

Conformer generation: The example cyclohexane

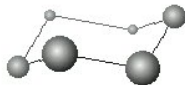
- The molecular graph has 12 automorphisms.
- We assume, that no 4 atoms are in a plane.
- We get 386 chirotopes.
- Excluding unfeasable radon partitions: 162
- Restricting to quadrupels corresponding to butane substructures: 13
- Conformation as local minima of an energy function were found for: 4
 - boat form (a "saddle point")
 - twist form



1234	1324	1423	2345	2435	1256	1456	3456
+	+	+	+	+	+	+	-
+	+	+	+	+	+	-	-
+	+	+	+	+	+	+	+
+	+	+	-	+	-	-	-

Conformer generation: The example cyclohexane

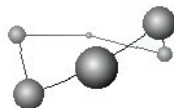
- The molecular graph has 12 automorphisms.
- We assume, that no 4 atoms are in a plane.
- We get **386** chirotopes.
- Excluding unfeasable radon partitions: **162**
- Restricting to quadrupels corresponding to butane substructures: **13**
- Conformation as local minima of an energy function were found for: **4**
 - boat form (a "saddle point")
 - twist form
 - chair form



1234	2345	1236	1256	1456	3456
+	+	+	+	+	-
+	+	+	+	-	-
+	+	-	+	+	+
+	+	+	-	-	-

Conformer generation: The example cyclohexane

- The molecular graph has 12 automorphisms.
- We assume, that no 4 atoms are in a plane.
- We get **386** chirotopes.
- Excluding unfeasible radon partitions: **162**
- Restricting to quadrupels corresponding to butane substructures: **13**
- Conformation as local minima of an energy function were found for: **4**
 - boat form (a “saddle point”)
 - twist form
 - chair form
 - twist form (enantiomere)



1234	2345	1236	1456	3456
+	+	+	+	-
+	+	+	+	-
+	+	+	+	+
+	-	+	+	+
+	+	+	-	-